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Objective evaluation of dextromethorphan and glaucine as antitussive agents

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1 Twenty-four inpatients affected by chronic cough completed a single-dose double-blind cross-over study of placebo, glaucine 30 mg and dextromethorphan 30 mg. The study was carried out using a balanced incomplete block design, each patient receiving two of the three experimental treatments.

2 Objective evaluation of cough was ensured by means of a writing cough recorder.

3 Coughs after dextromethorphan and glaucine were fewer than coughs after placebo: however only glaucine was significantly different from placebo in reducing coughs.

4 Treatments were well tolerated: clinical results included a reduction in pulse rate after both dextromethorphan and glaucine, and a large number of patients reporting side effects after dextromethorphan administration.

Keywords glaucine dextromethorphan antitussives

Introduction

The new antitussive agent (±)-glaucine 1, 5 phosphate (hereafter referred to as glaucine) is undergoing clinical studies to investigate its cough suppressant activity. The (+)-isomer of glaucine is an alkaloid which can be extracted from Glaucium Flavum Crants (Papaveraceae) and it has been used since 1967 in Eastern European countries as an antitussive agent (Stoykov, 1964; Chachaj *et al.*, 1972; Aleshinskaya, 1976). Synthetically produced racemic glaucine has shown interesting properties compared to codeine: lack of abuse potential in animals (Schuster *et al.*, 1982; Yanagita *et al.*, 1982); less respiratory depressant properties in human volunteers (Arnold *et al.*, 1980; Redpath & Pleuvry, 1982); similar antitussive activity in patients with chronic cough (Criscuolo, 1980; Dierckx *et al.*, 1981).

The aim of the present study was to evaluate with an objective recording system (Rühle *et al.*, 1977) the antitussive activity of single oral doses of glaucine as compared with dextromethorphan and placebo.

Methods

Thirty-two inpatients, affected by chronic cough caused by different underlying diseases, were selected to take part in the study. During the study, eight patients were excluded for various reasons, and therefore 24 patients completed the study: their characteristics are reported in Table 1.

Treatments to be administered were placebo, glaucine 30 mg and dextromethorphan 30 mg: they were supplied as 10 ml syrup in single-dose small glass bottles, identical in appearance and with a coded label indicating only the patient number and the night of administration (first or second). The Clinical Investigator had a sealed envelope with indication of the treatments: it was to be opened only in case of emergency, but this never occurred.

Treatments were randomized according to a balanced incomplete block design (in order to limit the discomfort caused by the throat microphone to only two nights) and were administered to each patient on two consecutive nights: therefore 16 observations were available after each of

Table 1 General characteristics of the 24 patients.

Sex	18 males + 6 females	
Age	Mean ± s.d.	53.0 ± 13.0 years
	Range	30 – 75 years
Body weight	Mean ± s.d.	70.1 ± 17.1 kg
	Range	40 ± 108 kg
Diagnosis	Pulmonary tuberculosis	= 6
	Bronchial carcinoma	= 5
	Pulmonary carcinoma	= 4
	Chronic bronchitis	= 4
	Bronchial asthma	= 3
	Obstructive bronchitis	= ·1
	Pulmonary silicosis	= 1

the three treatments. The experimental procedure was as follows: on each test evening the patient, after having his/her dinner, was accompanied to a quiet single-bed room equipped with the writing cough recorder (Rühle *et al.*, 1977). A contact throat microphone was externally affixed on the patient's larynx and wired to the recording unit. The microphone (a pressure transducer Siemens Elema AB-EMI 25C) was activated by coughs only, and not by background sounds or by the patient's voice: in a cough attack, every forcible expulsion of air was recorded as a separate cough. After an acclimatization period of about 1 h, the drug was administered and the recording started. Recording lasted overnight, approximately from 22.00 h to 06.00 h, for a total observation period of 8 h.

Evaluation parameters were: efficacy (antitussive effect): cough counts were obtained by means of the recorder, which provided figures divided into 1 h intervals. Moreover, on the morning after each test night, both the patient and the nurse on duty gave their blind evaluation on the cough during the night, selecting as appropriate from a 5 point scale (absent; mild; moderate; marked; very marked;) safety (clinical evaluation): the following parameters were monitored before and after each test night: respiratory rate, supine blood pressure, supine heart rate, standing blood pressure, standing heart rate. Moreover the onset and severity of the side effects were checked with a standard questionnaire.

Statistical methods

Partial and total cough counts were analyzed by the analysis of variance for balanced incomplete blocks according to the SAS program (Freund & Littell, 1981). Other safety measures such as respiratory rate, pulse rate and blood pressure, were analyzed by the paired *t*-test to detect any significant changes following drug administration (within the same treatment group). Two-tailed and 5% significance levels were applied in all the comparisons.

Ethical aspects

The protocol was reviewed and considered in accordance with the Declaration of Helsinki (1964) and the Tokyo revision (1975). Informed written consents were obtained by all the patients before admission to the study.

Drop-outs

Eight patients did not complete the study: reasons for discontinuing the study are discussed below.

Results

Total number of coughs after the three treatments were 689 after placebo, 511 after glaucine 30 mg and 540 after dextromethorphan 30 mg.

Mean values of coughs after the three treatments are depicted in Figure 1. They show the antitussive effect exerted by glaucine and dextromethorphan: in particular, the average number of coughs after glaucine is smaller than after the placebo in all but one interval (the 8 h cough count), and the mean number of coughs after dextromethorphan is smaller than after the placebo in all but three intervals (the 3 h, 4 h and 7 h cough counts).

Statistical analyses of these mean values do not reveal any significant difference, because of the high within-subjects variability. However, in the 1–6 h total cough count mean values after glaucine are definitely lower than after placebo, and this difference is statistically significant ($P < 0.05$).

Mean scores of both patient and nurse evaluation of cough, based on a 5 point scale (from absent to very marked) were practically superimposable: patient's mean scores were 2.9 after

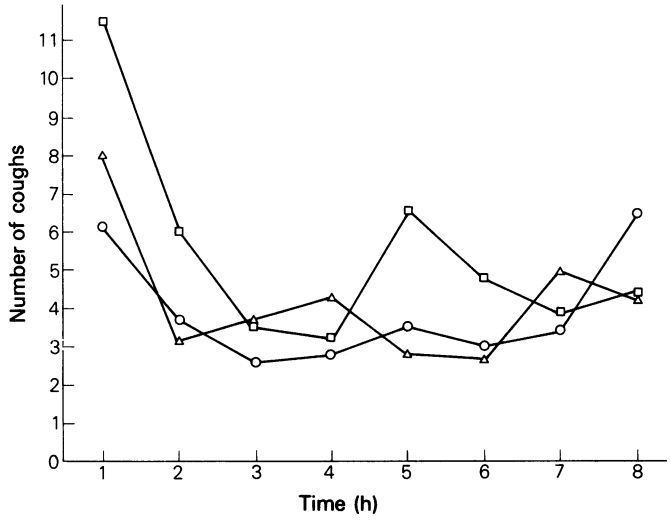

Figure 1 Mean number of coughs after the three treatments (□ placebo, △ detromethorphan 30 mg and ○ glaucine 30 mg) during the 1 h intervals of the observation period (n = 16).

placebo, 2.9 after glaucine 30 mg and 3.1 after dextromethorphan 30 mg.

Clinical data regarding the respiratory rate, blood pressure and heart rate, measured before and after drug administration, showed minimal variations: in particular, the difference between pre-treatment and post-treatment supine pulse rate was –5.5 ± 10.7 after placebo, –5.3 ± 7.5 after glaucine and –7.7 ± 10.8 after dextromethorphan. This difference was significant ($P < 0.05$) for glaucine and dextromethorphan.

Drop-outs

Eight patients did not complete the study for the following reasons: technical problems with the recorder during the first night (five patients), and refusal to undertake a second test night because of the discomfort caused by the microphone (three patients).

Side effects

Eleven out of the 24 patients who completed the study referred side effects. They are reported in Table 2.

Discussion

The experimental design to evaluate the clinical efficacy of an antitussive agent must follow some general rules such as the recruitment of patients with chronic cough, the use of a double-blind cross-over design and the inclusion of a placebo. The availability of a recording system which allows an evaluation of efficacy based on cough counts is mandatory. The lack of reliability of judgements about cough suppression expressed by patients has already been reported (Woolf & Rosenberg, 1964) and has been confirmed by the results of the present study.

Table 2 Incidence of side effects after the three treatments.

Side effect	*Placebo*	*Glaucine 30 mg*	*Dextromethorphan 30 mg*
Restless sleep	—	—	2
Headache	—	—	2
Blurred vision	—	—	2
Vomiting	—	1	1
Cough crisis	1	—	1
Diarrhoea	—	—	1
Asthma crisis	—	—	1
Sweating	1	—	—
Dizziness	—	—	1
Patients reporting side effects	2	1	8

Preliminary results from two clinical studies in which a cough recording system was applied (Criscuolo, 1980; Dierckx *et al.*, 1981) indicated that glaucine was as effective as codeine in suppressing chronic cough. The results of this clinical study are in accordance with these findings, and show that glaucine is significantly more effective than placebo in suppressing chronic cough caused by different underlying diseases.

Comparison of the results of a previous study performed in our Department (Matthys, 1982) with the results of the present study shows an interesting difference. In the former study the cough frequency in the placebo group decreased only from 10 to 8 coughs per hour, then remaining unchanged for the entire night; in the latter study the cough frequency in the placebo group was reduced to 3 coughs per hour, and then at about 03.00 h it increased again to 7 coughs per hour. The latter result is in agreement with the finding that cough frequency in patients without active treatment increases in the early morning (Gravenstein & Beecher, 1955).

The decrease in the pulse rate observed after administration of placebo, glaucine and dextromethorphan, which was significant only for the two active treatments, could be explained by taking into account the different times when measurements were taken: in fact pretreatment values were recorded in the afternoon, and post-treatment values were recorded in the morning of the next day. It is well known that the heart rate shows a circadian variation in both normotensive and hypertensive subjects with highest levels in the early afternoon and lowest levels in the early morning (Miller-Craig *et al.*, 1978).

Treatments were well tolerated: however, after administration of dextromethorphan several patients referred side effects such as restless sleep (2), headache (2), blurred vision (2), vomiting (1), cough crisis (1), asthma crisis (1), diarrhoea (1), and dizziness (1). On the contrary, after administration of glaucine only one patient reported a vomiting episode, and after administration of placebo there were two reported side effects such as cough crisis and sweating.

In conclusion the results of this study support the finding that glaucine is an effective antitussive drug which seems also to be better tolerated than dextromethorphan.

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